REMARKS

Upon entry of the foregoing amendment, claims 1-21 and 52-80 and new claims 81-84 are pending in the application. Claims 22-51 were withdrawn by the Examiner under 37 C.F.R. § 1.142(b) as being directed to a non-elected invention and have been canceled without prejudice to, or disclaimer of, the material recited therein. Claims 1-21 and 52-74, 76, 78 and 79 were rejected under 35 U.S.C. § 103. Claims 75 and 80 are stated to be free of prior art. Claim 77 was not designated as rejected or free of the prior art.

Support for the amendments to claims 1 and 63, reciting that the first promoter is a viral or eukaryotic promoter is found in the specification describing the types of promoters that may be used (see the specification at pages 17-19). Other amendments to the claims are supported by the previously filed claims. Accordingly, no new matter is added by the amendment of the claims.

The Rejection of the Claims Under 35 U.S.C. § 103 Is Traversed Or Rendered Moot

A. Prima Facie Obviousness

1. Claims 1-6, 8-10, 15-17, 52-53 and 61-62

The Examiner rejected claims 1-6, 8-10, 15-17, 52-53 and 61-62 as unpatentable under 35 U.S.C. § 103(a) in view of the combination of Cooper (U.S. Patent No. 5,719,055), Williamson et al., (Appl. Environ. Microbiol., 1994, 60:771-776), and Savakis et al., (U.S. Patent Publication 2003/0150007).

The Examiner cited Cooper as describing a vector encoding a transposase operably linked to a promoter, Mo transposon insertion sequences recognized by the transposase, an exogenous gene located between the transposon insertion sequences, and constitutive and/or inducible promoters regulating expression of the exogenous gene or the transposase. The Examiner cited Savakis et al. as describing the use of a "modified transposon," where the modification includes disruption of transposase sequences or the incorporation of one or more heterologous coding sequences and/or expression control sequences, tissue-specific and/or inducible promoters, and that the sequence of the transposase may be modified to optimize codon usage and thus, increase transposition frequencies. Also, the Examiner cited Williamson et al. as describing modification of the

5' end of a prokaryotic gene to include a eukaryotic start codon and Kozak sequence. Office Action at pages 4-5.

Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness for the reasons below.

The references fail to disclose elements of the claimed method

Applicants respectfully assert that the cited references do not, individually or in combination, teach or suggest a vector that uses a prokaryotic transposase gene (or any other prokaryotic gene) having a Kozak sequence of SEQ ID NO: 13 as the first codon, and a transposase gene modified such that a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein are individually modified from the wild-type sequence of cytosine or guanine at the third base position of the codon to an adenine or a thymine, such that the modification does not change the amino acid encoded by the modified codon and wherein the first promoter is a viral or eukaryotic promoter; and one or more genes of interest operably-linked to one or more additional promoters, wherein the one or more genes of interest and their operably-linked promoters are flanked by insertion sequences recognized by a transposase encoded by the modified transposase gene.

First, as amended, the claimed vectors include a viral or eukaryotic promoter driving expression of the prokaryotic transposase gene. In certain embodiments, the promoter driving transcription of the prokaryotic transposase is one of the vitellogenin, ovalbumin and/or conalbumin promoters. None of the references cited describe, teach or suggest using a eukaryotic promoter, and in particular, at least one of the vitellogenin, ovalbumin and/or conalbumin promoters to drive expression of a prokaryotic transposase gene.

Also, none of the references describe or suggested a transposase modified such that a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein are individually modified from the wild-type sequence of cytosine or guanine at the third base position of the codon to an adenine or a thymine, such that the modification does not change the amino acid encoded by the modified codon.

Applicants note that the reference Savakis et al., does not describe a vector having transposon sequences and a transposase, but describes a method whereby transposon

sequences are introduced into a first organism, the transposase is introduced into the second organism, and the animals are crossed to obtain transgenic progeny. Thus, there is no teaching in Savakis of how to construct a vector having such elements as a single nucleic acid construct. Instead, the constructs of Savakis et al. require breeding and crossing of genetic progeny to produce cells having the transposase and the transposons in some of the same cells. The approach and vector constructs used by Savakis are very different than the constructs used by Applicants where both constructs are on the same vector, but differential control is provided by the combination of regulatory elements. Nor, do the constructs of Savakis display the high level of efficiency which is surprisingly seen with Applicants' constructs as discussed in detail below.

Also, although Savakis et al., mention that the sequence of the transposase may be modified to **optimize codon usage for a particular host**, Savakis et al. explicitly states that optimization of codon usage is defined as converting codons that are used less frequently in the transgenic host organism to codons that are used more frequently in the transgenic host organism. Apparently, the Examiner is analogizing codon optimization as mentioned in Savakis to Applicants' modification of the N-terminus of the transposase gene. As asserted in Applicants' previous response, the optimization of codon usage that is described by Savakis et al. is **completely distinct** from Applicants' modification of the N-terminal first 10 codons to replace C or G at the wobble position with A or T. **Applicants are not optimizing codon usage for a particular host, but to facilitate strand dissociation during transcription**. See the specification at pages 14-15. If Applicants were modifying the transposase to optimize codon usage (e.g., to change the codons usage to codons used in chickens), the change in codons would not provide a plurality of A or T's at the first 10 codons, but would modify codons throughout the gene to increase usage of codons used by the chicken, quail, or other host organism.

The Examiner further stated that "modifying a plurality of first few codon and not the entire gene is also within the skills of one of ordinary skill in the art and it would be obvious to artisan that modifying first few codon would result in increased transcription. Office Action at page 11. Applicants vigorously assert that whereas the techniques of modifying a gene to change the sequence of codons are known to those of skill in the art,

there was no teaching in the art indicating that such a modification would have resulted in a functional transposon-based vector.

First, there is no teaching, suggestion, or motivation provided in the cited references (including the extremely limited disclosure of Savakis) to change the first 10 codons of the prokaryotic transposase gene in such a manner so as to have an A or T at the third position of the codon.

Also, there is absolutely no suggestion that such a change would be considered to optimize codon usage in avian or other animal hosts to increase either translation or transcription. In fact, as such sequences are not normally found in the host, there would be an expectation that such a change would not necessarily be successful.

Applicants remind the Examiner that an invention may not be deemed obvious where the prior art only provides an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992). Thus, the courts have held that an obviousness rejection may not be predicated on the view that the invention was "obvious to try," as for example, where the art gives only general guidance as to the particular form of the invention or how to achieve it. *In re Lindell*, 385 F.2d 453 (CCPA 1967), and *Ex parte Levengood*, 28 USPQ 1300 (Bd. Pat. App. & Inter, 1993).

Applicants respectfully note that under MPEP 2144.03, the Examiner should not rely on "common knowledge," but is required to provide documentary evidence that an aspect of the invention is common knowledge in the art. The Examiner has only provided a conclusory statement that the modification of the vector described and claimed by Applicants is the same as the concept of codon optimization for the purposes of increased translation in the host and that the techniques for making such a modification are known in the art. Applicants respectfully assert that the Examiner has not provided sufficient documentary evidence that the modification of a plurality of the first 10 bases of a prokaryotic gene, such that the third amino acid of each codon is A or T, without changing the amino acid encoded by the codon, is described, taught or suggested by Savakis or any other art.

There is no expectation of success

Also, although Williamson et al. describes the use of a Kozak sequence to promote the initiation of translation in a eukaryotic system, Williamson also states that "the lysostaphin gene joins a small group of prokaryotic genes which are known to be expressed in mammalian cells." Williamson et al. at page 775, col. 2. Thus, one reading Williamson et al. would not expect to be successful in expressing a prokaryotic transposase gene in eukaryotic cells. Nor would one be motivated to attempt to express a prokaryotic transposase gene in a eukaryotic host *in vivo*.

There is no motivation or reason to combine the references

Furthermore, there is no motivation or reason to combine Cooper with Savakis et al. and Williamson et al. to arrive at Applicants' invention. Cooper also teaches that a transposase-based vector may be designed **without using a transposase gene that has a Kozak sequence or is modified** from the wild-type sequence to include either an A or a T at the wobble position in a plurality of the first ten codons to promote strand dissociation of the transpose gene. Thus, one of skill in the art reading Cooper, would not be motivated to incorporate a Kozak sequence in a transposon-based vector, or to include a modified transposase gene, as these modifications were not required for transformation of mammalian and/or fish cells as described in Cooper.

For the reasons stated above, Applicants respectfully assert the Examiner is relying upon **hindsight** provided by Applicant's specification in that combined references do not teach each and every limitation of the invention of claims 1-6, 8-10, 15-17, 52-53 and 61-62, and that there is no suggestion or motivation to combine the references, or an expectation of success that the elements can be combined to provide Applicants' claimed invention.

2. Claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79

The Examiner rejected claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79 as unpatentable under 35 U.S.C. § 103(a) in view of the combination of Cooper, Williamson et al., and Savakis et al., further in view of Hackett et al., (U.S. Patent No. 6,489,458) and MacArthur et al. (U.S. Patent No. 6,825,396).

First, as amended the claimed vectors include a vitellogenin, ovalbumin and/or conalbumin promoter driving expression of the prokaryotic transposase gene. None of the references cited describe, teach or suggest using a eukaryotic promoter, and in particular, at least one of the vitellogenin, ovalbumin and/or conalbumin promoters to drive expression of a prokaryotic transposase gene.

The Examiner stated that Cooper, Williamson et al. or Savakis et al. do not teach the advantage of using ovalbumin or other egg-directing sequences, but that MacArthur et al. describe a vector comprising control elements that include an enhanced promoter to direct the expression of a gene in the oviduct, a 5' untranslated sequence, a signal sequence directing secretion in the egg-white, control sequences for liver expression, a signal sequence for egg yolk, as well as standard stop codons and a polyA sequence 3' to the structural gene. The Examiner stated that MacArthur et al. does not describe the use of these elements with a transposon, but cited Hacket as disclosing use of promotors (including an ovalbumin promoter) to express a transgene.

The references fail to disclose elements of the claimed method

Neither MacArthur et al., nor Hackett et al., disclose or **suggest** the use of **eukaryotic or viral promoters and signal sequences with a prokaryotic transposase**. MacArthur et al. does not describe transposon-based vectors, but describes retroviral vectors that may be used to transfect an embryonic chicken cell, so as to produce a transgenic hen having the transgene expressed in the hen's oviduct and the protein produced in the hen's eggs or the eggs of her offspring. The promoters, signal sequences, and other control sequences described by MacArthur et al. are only used with the exogenous gene and are not used to control expression of a prokaryotic gene (e.g., a prokaryotic transposase) in a eukaryotic cell. Thus, there is no teaching in MacArthur et al. of how to use such sequences with a prokaryotic transposase gene as recited in Applicants' claims and no reason to expect that the use of such eukaryotic control sequence could be used in combination with a proaryotic transposase.

As noted in applicants prior response, Hackett et al. describes using the Sleeping Beauty family of eukaryotic transposases as a system for introducing nucleic acid into the genome of a vetebrate cell and provides only a generic description that promoters and other regulatory elements may be used in transposon-based vectors. Hackett et al. does

not, however, describe, teach, or suggest that a eukaryotic promoter can be used with a prokaryotic transposase. Nor does Hackett describe the specific nucleotide sequences of constitutive and inducible promoters, enhancer elements, and signal sequences that may be used such as those described and claimed by Applicants.

There is no expectation of success

Also, in designing the SB transposase system, Hackett et al. specifically teaches that most transposases are species-specific, and that only the (eukaryotic) Tc1/mariner superfamily of transposases would be expected to be useful for cross-species transposition. Hackett et al., at col. 2, lines 6-14. Thus, Hackett **teaches away** from Applicants' invention. The U.S. Supreme Court and the Federal Circuit have held that it is improper to combine references where the references teach away from their combination. See *KSR International Co., v. Teleflex Inc.*, 127 S.Ct. 1727, at 1739-1740 (2007); *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983).

Thus, Applicants respectfully assert that without the hindsight provided by Applicants' application, the references of Cooper, Savakis et al., and Williamson et al., MacArthur et al., and Hackett et al., do not alone, or in combination (i.e., all of the references considered as a whole), describe, teach or suggest the invention of claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79.

3. Claims 1-21, 52-74, 76, 78, and 79

The Examiner rejected claims 1-21, 52-74, 76, 78, and 79 as unpatentable under 35 U.S.C. § 103(a), in view of the combination of Cooper, Williamson et al., Savakis et al., Hackett et al., MacArthur et al., and Wallace et al. (Biology: The Science of Life, 1986, Scott Foresman and Company, page 235). The Examiner cited Wallace et al. as teaching the use of stop codons (UAA, UAG and UGA) and double stop codons. Office Action at page 9.

The references fail to disclose elements of the claimed method

Applicants respectfully assert that Wallace et al. does not correct the deficiencies of the references discussed above. Applicants' claimed vectors comprise a **prokaryotic transposase gene operationally linked to a polyA sequence** and/or two stop codons (claims 12, 14, 54, 56, and 63). There is no description, teaching or suggestion provided

by Wallace et al. or other teachings (including MacArthur) in the art to include a polyA sequence that is operably-linked to a **prokaryotic** gene.

The Examiner has cited MacArthur as providing either a suggestion, description or motivation to use polyA sequences with a prokaryotic gene. Applicants have reviewed MacArthur, including the portions cited by the Examiner, and cannot find any suggestion, or description, or motivation to employ a **eukaryotic polyA** sequence in combination with a **prokaryotic gene**. MacArthur only describes the use of polyA sequences to ensure termination of the eukaryotic structural gene. See MacArthur at col. 9, lines 40-55, cited by the Examiner, Office Action at page 5. Applicants respectfully request that the Examiner explicitly describe where MacArthur provides such description, suggestion or motivation of the novel concept of using a polyA sequence to terminate transcription of a prokaryotic gene in view of the teaching **against** using such sequences as was known in the art (as outlined above).

Applicants again remind the Examiner that an invention may not be deemed obvious where the prior art only provides an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992), and that under MPEP 2144.03, the Examiner should not rely on "common knowledge," but is required to provide documentary evidence that an aspect of the invention is common knowledge in the art. The Examiner has only provided a conclusory statement that use of a polyA sequence 3' to a prokaryotic transposase gene would be expected to increase translation since such sequences are known to be downstream of eukaryotic genes (as noted in MacArthur). Applicants respectfully assert that the Examiner has not provided sufficient documentary evidence that such polyA sequences could be used downstream of a prokaryotic gene as has been described and claimed by Applicants.

There is no expectation of success

The Examiner has asserted that "one of ordinary skill in the art . . . would have been motivated to include . . . polyA as a obvious modification for expression in mammalian system" but has not provided any basis for this statement. Office Action at page 9.

As noted in Applicants prior response it is not taught or suggested in the art to add a polyA sequence to a prokaryotic gene. Thus, **most prokaryotic genes do not include polyA sequences**, and for the few prokaryotic genes that do include polyA sequences, the function of the polyA sequences is different than in eukaryotes. For these reasons, there was no expectation of success that a polyA sequence could be operably linked to a prokaryotic transposase gene and correctly positioned relative to the transposase gene and its associated stop codons. It was known in the art that improper positioning of the polyA sequence relative to a gene and its associated stop codons can result in a decrease in mRNA stability, resulting in less protein being produced. Further, a review of the literature indicates that it has not been possible to predict what sequence elements downstream of the stop codon, other than the polyA, are involved in stability, again indicating that there was no inherent expectation of success that it would be possible to operably link a polyA sequence to a prokaryotic gene. Thus, one would not be motivated to rely on the use of polyA sequences to increase expression of a prokaryotic gene as it was not clear as to whether such an approach would be successful.

Applicants respectfully assert that without the hindsight provided by Applicants' application, the references of Cooper, Savakis et al., and Williamson et al., MacArthur et al., Hackett et al., and Wallace et al., do not alone, or in combination (i.e., all of the references considered as a whole), describe, teach or suggest the invention of claims 1-21, 52-74, 76, 78, and 79. For at least these reasons, Applicants respectfully assert that pending claims 1-21, 52-74, 76, 78, and 79 are not *prima facie* obvious under 35 U.S.C. § 103, and respectfully request that the rejection be withdrawn.

B. Secondary Considerations

Additionally, as noted in Applicants' prior response, secondary considerations render the claimed invention as not obvious over the cited references. The Examiner noted that the cited references exemplified the art recognized goal to improve efficiency of vectors used for avian trangenesis. Thus, there was an **unsolved need** for Applicants' for vectors, and in particular transposon-based vectors that have improved efficiency of transposition and that can be used for avian transgenesis, which are provided by Applicants' invention.

The Examiner appeared to question whether the results provided by Applicants' September 26, 2006 declaration could be used to provide an indication of the increased integration frequency provided by Applicants' vectors. Applicants note that the vector used in the experiments was the TnMod vector. Applicants have used this vector in numerous experiments (varying promoter elements and genes of interest) and have consistently shown integration frequencies that are an order of magnitude greater than the vectors of the prior art. Thus, as explicitly stated in the specification at page 13, lines 15-23, the vectors of the present invention produce integration frequencies an order of magnitude greater than other vectors commonly used at the time of the invention and almost a 2-fold increase in insertion frequency over the vectors of Cooper.

Additionally, Applicants' Declaration Under C.F.R. § 1.132, filed on September 26, 2006, showed that using a vector of the invention (pTnMod as described in Example 1 of the specification) with a monoclonal antibody encoded by the gene of interest resulted in very high efficiencies in transfecting both the livers and ovaries of female quails that were injected via a cardiac route. Applicants are not aware of any other vectors that approach this level of efficiency. The vectors used in the experiments described in the Declaration include a Kozak sequence positioned to include the first codon of the transposase, a modified transposase gene having a plurality of the codons of the transposase gene that encode for amino acids 2-10 of the transposase protein modified from the wild-type sequence of cytosine or guanine at the third base position of the codon to an adenine or a thymine such that the modification does not change the amino acid encoded by the modified codon, as well as two stop codons, and a poly A sequence operably linked to the transposase.

Further, Applicants respectfully assert that it is the unique combination of elements provided by Applicants' vectors that enable the vectors to transfect cells in a live animal to produce chimeric animals in the G0 generation and expression of exogenous proteins in the egg white of eggs produced by the chimeric animal. This allows for production of animals that can produce transgenic proteins without having to go through two successive generations of breeding (from G0 to G2). Applicants are not aware of any other vectors that provide this capability. Applicants note that Cooper, MacArthur et al., and Hackett et al., each describe the use of such vectors for the direct

transfection of eggs for hatching and eventual production of G2 transgenic animals. Thus, there is no teaching or suggestion in any of the cited references that such elements may be used to control the expression of a prokaryotic transposase gene in a eukaryotic cell, or how such elements may be combined to produce a vector that is able to generate G0 chimeric and/or G1 transgenic animals.

Thus, Applicants respectfully assert that the pending claims are not obvious under 35 U.S.C. § 103, and respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

Date: October 31, 2007

Cynthia B. Rothschild (Reg. No. 47,040)

KILPATRICK STOCKTON LLP
1001 West Fourth Street
Winston-Salem, North Carolina 27101-2400
Phone: (336) 747-7541
Facsimile: (336) 607-7500